
CONTRIBUTIONS OF THE
U.S. PUBLIC HEALTH SERVICE
IN TROPICAL MEDICINE: PART II*

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It has been indicated in a previous presentation that the early interest of the Public Health Service in tropical diseases, and its early contributions to that field, stemmed from the operation of the Marine Hospital Services. The history of yellow fever in this country, which has already been reviewed, reflects this fact, particularly in the early studies done by Henry Rose Carter and his group at the New Orleans Marine Hospital. Their investigations on the epidemiology of the disease, prior to the revelation of the role of the mosquito, are classics. It was at about this same time, i.e., the early 1900's, that interest in research and control of malaria arose in North America, and I should like to spend the next few minutes on the accomplishments of the following 50 years in this field.

It is probable that the first organized studies of the Public Health Service on malaria were begun in 1912 by Dr. Carter and his associates. These early efforts were made against a background of extreme optimism, born of the successes of William C. Gorgas in Panama, Oswaldo Cruz and Carlos Chagas in Brazil, and Malcolm Watson in the Federated Malay States. With this background the reduction and control of malaria appeared to be a fairly simple matter, and a dedicated group of workers, including Carter, J. A. Le Prince (who had been one of the architects of the control programs in Cuba and Panama), T. H. D. Griffiths, R. H. von Ezdorf, R. C. Derivaux, C. W. Metz, and many others attempted to show by demonstration and by education that malaria could be curbed by using the knowledge already at hand. Their methods included the entire gamut: treatment, larvicid-

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ing, ditching, drainage, screening, and management of water level. It is probable that all these workers were convinced that malaria could be controlled and even eliminated as a significant problem. Indeed, the term "malaria eradication" had turned up in 1915. It is interesting that even Charles Wardell Stiles, the eminent zoologist, made at least one excursion into the South to assess the problems of mosquitoes and malaria and to make recommendations for solution of the problems.

With the advent of World War I the Public Health Service became active in programs for control of the mosquito in areas adjacent to military bases, and there was a notable quantitative increase in operations for control, if not a qualitative one. There is little doubt that the expansion of operations during the war served a valuable purpose by involving large numbers of workers who were to continue to work in the field of malaria control and research and who would make significant contributions to the field during the next several decades.

Research on larval control methods during the war culminated in 1921 in the development by M.A. Barber and T. B. Hayne of paris green as a larvicide. This was to be the larvicide of choice for the next 25 years; its widespread use around the malarious world was an important factor in many programs for the control of mosquitoes.

Research on malaria was continued under the auspices of the Public Health Service through the early 1920's, with continued emphasis on demonstration of the control of malaria and of mosquitoes, and on surveys to determine the extent and on surveys to determine the extent and severity of the malaria problem in the United States.

Much of this work was done in cooperation with the International Health Board of the Rockefeller Foundation, which had become interested in the control of malaria prior to the war. The Public Health Service can claim some credit in bringing the International Health Board into the malaria field. In 1915 the International Health Board requested the assistance of the Public Health Service in selecting appropriate problems. The Public Health Service invited the board to participate in a demonstration project on malaria control in Crossett, Ark., a small lumbering community. After several very successful years of work there, the International Health Board adopted the control of malaria as one of its major projects and participated widely with the Public Health Service in further demonstration projects and educational activities in this country. During the 1920's and 1930's the Rockefeller

Foundation supported and maintained a program of malaria research and control, which enlisted the talents of outstanding workers in the field, such as Paul F. Russell, L. W. Hackett, Mark F. Boyd, R. B. Hill, W. C. Earle, Fred L. Soper, L. T. Coggeshall, and others. This program was not confined to the United States but operated in many other areas of the world as well. There seemed to be a growing realization during the early 1920's that malaria control was not a simple matter and that we needed to know a great deal more about the parasite, the disease, and the vector before we could reasonably expect wide success. The record of accomplishment of the Rockefeller group in its world-wide investigations, both in the field and in the laboratory, is enviable.

There seems to be little doubt that true malaria research under the auspices of the Public Health Service had its beginning in 1927 in a program instituted by L. L. Williams, Jr. Dr. Williams was a person of rare vision who believed that malaria could be controlled and even eradicated, but he realized at the same time that there was a continuing need to conduct research and to learn everything possible about the parasite and its hosts. Whatever has been accomplished by the Public Health Service in malaria research and control during the past 35 years or more can be attributed directly or indirectly to the vision and energy of L. L. Williams.

In 1931 Dr. Williams established a malaria research laboratory at the South Carolina State Hospital in Columbia; this laboratory was under the direction of Bruce Mayne until Mayne's death, and then under the direction of Martin Young from 1941 to 1961. The use of malaria as a form of treatment for cerebrospinal syphilis had been established in 1918; this use gave promise of an opportunity to learn a great deal about malarial infection in man. A laboratory for research in this connection was established in the early 1920's in England at the Horton Hospital with outstanding success; the laboratory at Columbia, S.C., and a similar installation at Tallahassee, Florida, under the sponsorship of the Rockefeller Foundation and directed by Mark Boyd were similarly successful and contributed enormously to the fund of knowledge on malaria in man.

The malaria research programs of the National Institutes of Health had their beginnings in the Columbia Laboratory, in a Laboratory of Malaria Investigations in Memphis, Tenn., and several small groups in Washington, D.C., concerned with chemotherapeutic studies or with

the diagnosis of the infection in man. It might be pointed out that the standard manual for the microscopic diagnosis of malaria was written by Aimee Wilcox as a part of this latter program. With the advent of World War II came an expansion of effort by the Public Health Service on a number of fronts.

One of the greatest concerns at the beginning of the war was for sufficient chemotherapeutic agents to control malaria in the units engaged in the South Pacific and other intensely malarious areas of the world. The supplies of quinine had been all but cut off; atebnine was not well known and, at the beginning of the war, it was suspect insofar as its side effects were concerned. A Board for the Coordination of Malarial Studies was established by joint action of a number of agencies. William H. Sebrell, Lyndon F. Small, and G. Robert Coaney represented the Public Health Service and the National Institute of Health (NIH) on this board. This board was instrumental in stimulating an enormous amount of work on the chemotherapy of malaria during the war years. Chemotherapeutic studies at the NIH had been initiated in 1938 by Maurice Roe and Dr. Small. In 1941 the program was enlarged enormously and placed under the direction of G. Robert Coatney; during the war years thousands of compounds were run through the *Plasmodium gallinaceum*—chicken screen—at this and other locations. In 1944 it was apparent that the major deficiency in the program of drug development was the shortage of potential for testing promising compounds in man under carefully controlled conditions. Therefore, in 1944 a project was established by NIH in cooperation with the Department of Justice at the Atlanta Federal Penitentiary, where volunteers were allowed to participate in the evaluation of new compounds against induced malaria infections. This program has been continued at Atlanta, Ga. or at federal institutions elsewhere with virtually no interruption until the present. Let us hope that it will continue until we have reasonably good solutions for our chemotherapeutic problems. Over the years this has been an eminently successful program; about 3,000 volunteers have participated in it, and every useful and effective antimalarial compound developed during this period has received its final or confirmatory trials within this project. A similar project established at about the same time by Alf Alving of the University of Chicago has been similarly successful and productive. Among the accomplishments of these units have been: 1) the evaluation of

chloroquine and the other 4-amino-quinolines, which have established dosages and regimens that are essentially those in use today; 2) exploration of the 8-amino-quinolines, with final determination that primaquine is the most effective one, and establishment of standard methods of treatment with this drug; 3) the development of pyrimethamine as a usable and efficient antimalarial; 4) determination of the effectiveness of the long-acting repository compound CI-501 (or cycloguanil pamoate); and many others.

We are now faced, of course, with the severe problem of drug-resistant strains of falciparum malaria, and the program for its solution continues to be invaluable in the search for temporary and permanent chemotherapeutic alternatives and in characterizing the spectrum of drug resistance in many of the strains.

Studies at the laboratory in Columbia, S.C. continued through the 1940's and 1950's under the direction of Martin Young; from 1946 to 1954 a similar installation was operated at the Milledgeville, Ga., State Hospital. One serious concern during World War II was the possibility that more virulent strains of *Plasmodium* would be introduced into this country, which would have worsened the malarial situation that already existed. A series of studies were undertaken on imported malarias, characterizing them in the human and mosquito hosts, determining their transmissibility through the local anophelines, and otherwise assessing their threat to this country. During this period several additional field stations were established at military bases within the United States. In subsequent years many significant studies were done on the biology of malaria infection in man and mosquito, the response of infections to various regimens of drugs and treatment and the cytology of the malaria parasites. Within this paper it is not possible to do justice to the range and extent of the studies on the human and experimental malarias that have been done. If published reports can serve as a criterion of productivity, the Columbia laboratory was responsible for more than 200 such reports on research during the last 20 years of its existence.

The basic studies on malaria which have been done at the several laboratories of the NIH have been supplemented from time to time with field programs in various parts of the world. This has been a most important part of the program, and it has allowed staff members to contribute to some of the practical applications of their findings.

One of the most recent programs has concerned the simian malarias as zoonoses in man. After accidental transmission of one of the malarias found in a monkey (*P. cynomolgi*) to several members of the laboratory staff in the course of studies on mosquito-induced infections, an intensive program was launched in the laboratory and in the field, in Malaysia, to determine to what extent malaria in monkeys may be important as zoonoses. This has been a model of a combined laboratory, clinical, and field investigation. In a relatively short time it has yielded more information on the ecology of the simian malarias and on their relation to man than had been developed during the prior 50 years. A number of new species of malaria were described; natural vectors of these malarias were described for the first time; man was experimentally infected by inoculation through a mosquito with at least four additional species of malaria from nonhuman primates—*P. inui*, *P. brasiliannum*, *P. knowlesi* and *P. schwetzi*. Moreover the first actual case of a simian malaria—*P. knowlesi*—contracted by man in the field was reported, confirming the parasite as a true zoonosis. Perhaps most important, a variety of simian malarias, simulating very closely all of the human malarias, have become available as very good experimental models for the study of the disease in the primate host.

Meanwhile—to go back a few years—significant progress was being achieved in the late 1930's in the control of malaria in the United States. L. L. Williams, Jr., had designed a plan for the control of malaria in the affected states and provided the needed leadership to place this plan in operation. By the time this country had become involved in World War II good state organizations and malaria control units had been established, and these, under the leadership of the Public Health Service, provided the nucleus for wartime operations for the control of malaria. The office of Malaria Control in War Areas (MCWA) was established to coordinate the efforts of the state and local governments with those of the Public Health Service and the armed services for control of malaria in critical areas in this country. Through this agency the Public Health Service provided funds, personnel, training programs, and other material and advisory assistance to the states.

To shorten a long story of accomplishment: the control of malaria during the war years was eminently successful; there was no significant increase in endemic malaria following the return of veterans from malarious areas and their inevitable importation of new strains. In fact,

the normal rise of malaria rates predicted for the early 1940's failed to materialize.

After the war the Public Health Service, functioning through the Communicable Disease Center, successor to MCWA, committed its resources to an "extended program" of malaria control; it proposed to utilize the new insecticides and methods of residual application in house spraying, for it was felt that the time was ripe for complete eradication of the disease in this country. There seemed to be some reluctance to use the term "eradication," but in 1947 the semantic facade was dropped and the National Malaria Eradication program was officially established, just in time to preside over the disappearance of the disease. This was officially proclaimed in 1951 when, according to standards set up by the National Malaria Society, malaria was declared eradicated in the United States. Whether it had been eradicated or merely disappeared is academic. It is clear that whatever success had been achieved in this effort gave courage to health workers elsewhere, and the eradication of malaria as a worldwide goal was adopted by the World Health Organization in 1955. The contributions of the Public Health Service to this endeavor are probably greatest in the area of technical developments in the methodology of using insecticides. In the years since the cessation of direct involvement of the Public Health Service in programs of control in this country, it has supplied technical advisors to our own foreign aid agencies that have interest in the eradication of malaria abroad, and to the international agencies—the Pan American Health Organization and the World Health Organization. The Communicable Disease Center has maintained a technical development laboratory which has been active in the development of new insecticides and new methods of application, and in the definition of the limitations of these methods in the face of resistance to insecticides shown by mosquitoes and in other severe problems encountered in the field.

Recently the Communicable Disease Center (CDC) has been given the direct responsibility of staffing and operating the technical program for the interests of the U.S. Agency for International Development, in the eradication of malaria. With characteristic energy and enthusiasm, CDC is establishing a program which has great promise for benefiting not only the projects with which they will be directly concerned, but also efforts to eradicate malaria everywhere.

Perhaps the chief contribution of the Public Health Service in the

field investigations and control of malaria has been the rather stable maintenance of at least a small nucleus of competent personnel for over 50 years. This has been possible through the dedication of a number of individuals who have actively worked in the research and control of malaria, and through the support of program directors and policy makers who have had the foresight to support these endeavors. Even in the early 1900's malaria could not be considered high on the list of medical problems in this country, and there were difficulties in gaining support for work on this disease. One can easily imagine the difficulties involved in supporting malaria research against a background of attempts to eradicate malaria in this country and in an era that was overly optimistic about eradicating it throughout the world. In the period between the Korean conflict and our current southeast Asian problems, research on malaria dropped to a low ebb; virtually its entire support came through the NIH-CDC intramural research programs or through the extramural grant program of the NIH. In spite of the heroic efforts of a few to maintain a respectable level of research and training in the problem of combatting malaria and other parasitic diseases, the number of competent workers in the field has been dwindling; the schools which formerly produced and trained our parasitologists and malariologists are turning out fewer and fewer such men. It is perhaps unfortunate that the only major stimulus to increase studies in malaria at present is our military involvement in southeast Asia, where problems of malaria hyperendemicity and of drug-resistant parasites are almost insurmountable. This expansion of work has been achieved primarily through the armed forces, and it represents a significant effort. One can hope that it will continue to produce information in needed areas of research, for example as to new chemotherapeutic agents or as to pathological and immune processes in the host, and that it will also leave us a legacy of competent people interested in continuing studies in this important area.

Although this presentation appears to be preoccupied with malaria, important contributions have been made by the Public Health Service in the investigation of other protozoan diseases.

The first work reported on amebiasis was just after World War I, when W. C. Boeck and C. W. Stiles did a survey on the prevalence of the infection in overseas veterans. George McCoy of the NIH was active in investigating the Chicago epidemic of amebic dysentery of

1933, and during the 1930's there were active amebiasis units maintained jointly by the NIH at the University of Chicago and Tulane University. In 1940 more intensive studies were initiated at the NIH in Bethesda, and during subsequent years there were a number of important contributions in this field of study, particularly in the cultivation and characterization of various strains and on the pathogenicity of the infection in various laboratory hosts.

These studies by C. W. Rees, Lucy V. Reardon, F. J. Brady, and many others contributed greatly to our present-day knowledge of this infection. More recent studies by Morris Goldman, L. S. Diamond, and others have contributed to the characterization of various strains and races of the parasite, showing morphologic, physiologic, immunologic, and antigenic differences. This work has resulted in the revision of speciation of the parasite and has suggested corresponding differences in pathogenicity of the several forms.

A program of study of toxoplasmosis was initiated in the late 1940's at the NIH laboratories in Bethesda under Leon Jacobs and his associates, and at Memphis, Tenn., by the late Don E. Eyles and his group. Significant advances were made by these two groups, who proved that *Toxoplasma* was a cause of chorioretinitis, who developed a hemagglutination test for diagnosis and developed the first and only effective treatment for the disease. Further contributions were made through field and laboratory studies to the knowledge of the epidemiology and epizootology of the infection and of the biological characteristics of the causative organism.

In the interest of economy of space it is not possible to cover completely all of the research done under auspices of the Public Health Service on the protozoan parasites. It is probable that no such parasite of importance has been overlooked. Perhaps more important than the studies of the individual parasite species have been the numerous investigations covering the entire field of parasitology. These investigations have been undertaken by such men as Theodor von Brand who, with his associates, has studied the physiology and biochemistry of parasitism for more than 20 years; or John Bozicevich, who contributed significantly in the area of immunodiagnosis of parasitic diseases during his long association with the NIH.

Unfortunately, it has been necessary in this presentation to ignore completely many significant contributions of the PHS to tropical medi-

cine outside of those dealing with the parasitic diseases. Nothing has been said of the early pioneering work of Joseph Goldberger and his associates on pellagra and other nutritional deficiencies—certainly a most important contribution. The PHS has been the moving force in campaigns for the elimination of yaws, immunization against smallpox and measles, antituberculosis campaigns, and cholera investigations and control. Certainly the work of the Rocky Mountain Laboratory on the vectors and epidemiology of rickettsial and viral diseases cannot be overlooked. The Service had early interests in and was active in significant investigations of plague and typhus in this country and in many other parts of the world. The introduction of the use of the sulfones for the treatment of leprosy by Guy H. Faget and his co-workers at the Carville Leprosarium represents another significant contribution.

It seems quite likely that one could continue *ad infinitum* enumerating individual contributions of the PHS to the body of knowledge on the so-called tropical diseases. Short of an extensive volume there seems to be little hope of completeness. One can hope that this proud record of accomplishment will continue, and that there will be a continuous realization that the ills of the tropical areas are not unimportant to the future well-being of the entire world.